

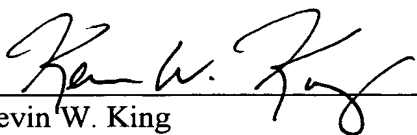
Remarks

The specification has been amended to reference the priority application.

Claims 1-20, as shown in the published PCT application with amended sheets 22-24 attached to the response to second written opinion, are pending prior to entry of this Preliminary Amendment. Claims 18 and 20 have been canceled, and claims 1-17 and 19 have been amended to eliminate multiple dependencies, to use Markush groups where appropriate, and to clarify the claimed compositions and methods. New claims 21 and 22 have been added. Support for these claims is found at least on page 7, lines 2-4 and lines 11-13. No new matter has been added.

Allowance of claims 1-17, 19, 21, and 22 is earnestly solicited.

Respectfully submitted,



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APPENDIX
Claims as Preliminarily Amended

1. (Amended) A controlled release composition [including] comprising pellets, wherein each pellet [comprising] comprises an inner core[, which core comprises, or is coated with,] comprising a drug[, which drug] which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

[which] wherein the inner core is [subsequently] coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. (Amended) [A composition as claimed in Claim] The composition of claim 1 wherein the drug is a thromboxane synthase A₂ inhibitor or a thromboxane A₂/prostaglandin endoperoxide receptor antagonist.

3. (Amended) [A composition as claimed in Claim] The composition of claim 2 wherein the drug is ridogrel.

4. (Amended) [A composition as claimed in any one of Claims 1 to 3,] The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. (Amended) [A composition as claimed in Claim 4,] The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. (Amended) [A composition as claimed in Claim 5,] The composition of claim 5 wherein the rate-controlling membrane is formulated from [ethylcellulose or Eudragit] EUDRAGITTM NE30D.

7. (Amended) [A composition as claimed in Claim 6 where] The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the inner core is a sugar sphere.

9. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. (Amended) [A composition as claimed in any Claim 9,] The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. (Amended) [A composition as claimed in any one of the preceding claims,] The composition of claim 1 wherein the salt is an alkali metal salt.

12. (Amended) [A composition as claimed in Claim 11,] The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. (Amended) [A composition as claimed in any one of the preceding claims] The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. (Amended) [A composition as claimed in any one of the preceding claims] The composition of claim 1 wherein the drug is used for [the] a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. (Amended) A [process] method for [the preparation of] making a composition [according to any one of the preceding claims which comprises] comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising

making a salt of the drug, and

coating [said] the salt onto the inner cores.

16. (Amended) [A process as claimed in Claim 15,] The method of claim 15 wherein the salt is prepared as part of a preparation process for the coating of the inner cores.

17. (Amended) A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, [which comprises administering a composition according any one of Claims 1 to 14 to a patient, preferably a human patient] the method comprising administering the drug in a composition comprising pellets, wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

18. (Cancelled).

19. (Amended) A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, [which method comprises] the method comprising

administering to a patient in need of treatment a composition [according to any one of Claims 1 to 14 to a patient, preferably a human patient] comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

20. (Cancelled).

21. (New) The composition of claim 1 wherein the pellets are compressed into tablets which are coated to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. (New) The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.